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EXAMINER	
SHIBUYA, MARK LANCE	
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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
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Shibuya	
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Commissioner for Patents

The attached Examiner's Answer corrects formal matters in regards to paragraph (8), Evidence Relied Upon, and merely lists the references of record relied upon in the rejection of record. No arguments, rejections, or references are added.

Mark L. Shibuya, Ph.D.
Primary Examiner
Art Unit: 1639

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/457,926
Filing Date: December 08, 1999
Appellant(s): CHRISTENSEN ET AL.

Sanya Sukduang
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief, filed July 13, 2006, appealing from the Office action mailed November 21, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,693,791	TRUETT	10-1997
6,437,11	TRUETT	8-2002

Boeckh, M. et al. "Pharmacokinetics and Serum Bactericidal Activity of Vancomycin Alone and in Combination with Ceftazidime in Healthy Volunteers", Antimicrob. Agents Chemother., vol. 32, no. 1, (Jan. 1988), pp. 92-95.

Renoud-Grappin, M. et al. "Imidazo[1,5-b]pyridazine-d4T Conjugates: Synthesis and Anti-Human Immunodeficiency Virus Evaluation", Antiviral Chem. & Chemotherapy, 1998, vol. 9, no.3, pp. 205-221.

Staroske, T. et al. "Synthesis of Covalent Head-to-Tail Dimers of Vancomycin", Tet. Lett., vol. 39, (1998), pp. 4917-4920.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 41, 43, 49-51 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Truett, US 5,693,791**, (hereinafter "Truett I"), in view of **Truett, US 6,437,119**, (hereinafter "Truett II"), (priority to May 7, 1998); and **Boeckh et al.**, Antimicrob. Agents Chemother., 1988, Vol. 32, No. 1, pp. 92-95; and **Renoud-Grappin et al.**, Antiviral Chem. and Chemotherapy, Vol. 9, No.3, 1998, pp. 205-221; and **Staroske et al.**, Tet. Lett., 1998, Vol. 39, pp. 4917-4920.

Truett I, US 5,693,791, teaches the "linking of diverse antibiotic moieties via difunctional organic compounds" (see column 1, lines 8-9). Specifically, dimers are taught having the structure A-L-B, where A and B are various antibiotic moieties (see "Summary", columns 1-6, especially column 1, lines 46-64). A variety of linkers and

linkage chemistries are taught (see columns 25-32). The reference teaches that the linkage of two antibiotic moieties can create compounds of new activity (see column 1, lines 1-30) and that "two antibiotic moieties can be linked in which one is known to attack Gram positive bacteria and another to attack Gram negative bacteria" (see column 1, lines 27-30). Truett I teaches a dimeric compound where one of the antibiotic moieties is ceftazidime (see column 3, line 7). Ceftazidime is a beta-lactam antibiotic that reads on the elected species that is set forth in claim 53, see structure in the instant Figure 6B-2.

Truett I lacks the teaching of linking vancomycin with ceftazidime.

Truett II, US 6,437,119, throughout the patent and abstract, teaches linking antibiotics by internal reactions to give three linked antibiotics for controlling infections via suppressing DNA replication, cell wall formation and protein synthesis. Truett II, US 6,437,119, at col. 1, lines 12-21, col. 2, lines 26-34, col. 2, line 65-col. 3, line 47, and col. 26, lines 48-56, teach making and using compounds having three antibiotic functionalities linked together, where a quinolone derivative is linked to a beta lactam, which, in turn, is linked to vancomycin. Thus Truett II, US 6,437,119 teaches linking a beta-lactam antibiotic to vancomycin in an antibiotic compound.

Truett II, US 6,437,119, is a continuation in part of US Application No. 09/304,715, filed 5/4/1999, and claims benefit of Provisional Application No. 60/084,586, filed 5/7/1998.

It was well known in the art at the time of filing to use combination therapy with vancomycin and ceftazidime. For example, **Boeckh et al.**, teach that this combination

therapy is used to "cover a broad spectrum of gram positive and gram negative bacteria", (see Boeckh et al., at page 92, first paragraph). The reference teaches the pharmacokinetics of the combination of vancomycin and ceftazidime, administered to humans (see Boeckh et al., at the Abstract and Table 1), thus pharmaceutical compositions of the drugs are well known.

Renoud-Grappin et al., teach that one way to achieve effective combination therapy is to covalently link two different drugs. See Renoud-Grappin et al., at p. 208, first column, first full paragraph of the reference, which describes using heterodimers for combination therapy linked "through an appropriate spacer, in an attempt to combine the inhibitory capacity" of two different classes of molecules. The reference also describes that one would attempt such an approach to span two binding sites on the target. Renoud-Grappin et al., also discusses combining different drugs to "prevent the emergence of drug-resistant virus strains" and sets forth three main reasons for combination therapy (see p. 207, second column, second paragraph). It is recognized that the linked compounds of Renoud-Grappin et al., (see, e.g., Renoud-Grappin et al., at Figure 4) are anti-virals and not antibiotics; however, it is the examiner's position that one of ordinary skill in the art would recognize the relevance of preventing the emergence of drug-resistant strains for both classes of molecules since such was well established in the art.

Additionally, vancomycin dimers were also known in the art at the time of filing. **Staroske et al.**, discuss both "head-to-head" and "head-to-tail" dimers (see Staroske et al., at Figure 3) and that in "light of recent reports of vancomycin-resistant bacteria"

there is a "strong incentive for the development of more potent antibiotics" (Staroske et al., at p. 4917, bottom). The reference also teaches that dimeric vancomycin compounds exhibit improved antibacterial activity, (see, e.g., Staroske et al., at p. 4918, top). Specifically, the dimers of Staroske et al., are linked from the amino terminus of one vancomycin moiety to the carboxy terminus of another (see, Staroske et al., at Scheme 1, p. 4919). The reference also contemplates linking of the vancomycin at the vancosamine moiety (see Staroske et al., at p. 4920, last two paragraphs).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to link vancomycin and ceftazidime, based on the teaching of Truett I, US 5,693,791, concerning the linking of diverse antibiotic moieties, and Truett II, US 6,437,119, where vancomycin and beta-lactam antibiotics are linked as part of a linked, three antibiotic compound, combined with the teaching of Boeckh et al., to perform combination therapy using the drugs, the teaching of Renoud-Grappin et al., concerning linking drugs to perform combination therapy and the teaching of Staroske et al., concerning vancomycin dimers linked through the amino and carboxy terminus. Specifically, the reference of Truett I, US 5,693,791, teaches that two antibiotics, one known to attack Gram positive bacteria and another to attack Gram negative bacteria, can be linked and the advantages of doing such, and Boeckh et al. teaches that vancomycin and ceftazidime fulfill these requirements. Furthermore, Truett II, US 6,437,119, teaches linking vancomycin and a beta-lactam as part of a three compound antibiotic. Renoud-Grappin et al., teach that one way to achieve effective

combination therapy is to covalently link two different drugs. Finally, Staroske et al. teach that vancomycin can be linked at specific linkage sites.

One of ordinary skill would have been motivated to covalently link vancomycin with ceftazidime to create a broad spectrum antibiotic compound to fight antibiotic resistant strains.

One of ordinary skill would also have had a reasonable expectation of success based on the fact that the references of Truett, US 5,693,791 and Truett US 6,437,119 and Staroske et al. teach linking chemistry for vancomycin and beta-lactam compounds.

Maintained Responses to Arguments filed 6/28/2005

Appellant, in the Reply, entered 6/28/2005, (hereinafter "Reply"), e.g., at p. 6, argues that a prima facie case of obvious has not been established because there exists neither suggestion nor motivation to combine and modify the five references relied upon in the rejection in the manner proposed by the examiner.

In Section 1, in regards to the reference of Truett I, US 5,693,791, appellant argues that the examiner must provide a basis for the initial selection of a single one of the 69 specific compounds (distributed among 9 classes of compounds) disclosed in Truett I, i.e., ceftazidime, from among all the other antibiotic compounds disclosed in the reference. Appellant argues that "after consideration of the teaching of Truett I as a whole, the reference does not contain the specific guidance needed to suggest the selection of ceftazidime over all the other disclosed antibiotics", (Reply at p. 7, para 3).

Appellant argues that that Truett I "was filed at a time when vancomycin was well-known in the art, i.e., 1995, yet fails to mention vancomycin or even the general

class of antibiotics to which it belongs. Appellants therefore submit that a reading of Truett I as a whole would not have motivated one skilled in the art to modify Truett I to combine vancomycin with any of the 9 disclosed classes of antibiotics, let alone combine vancomycin with ceftazidime, one of the 69 specifically disclosed compounds, in an attempt to arrive at the presently claimed invention." Reply at p. 8.

In Section 2, in regards to the reference of Truett, US 6,437,119, which appellant refers to as Truett II, appellant argues that, "Truett II, at best, discloses the linking of a third antibiotic, such as vancomycin, to a bicomponent compound that already contains a quinolone moiety linked to a beta-lactam moiety. Such a disclosure can be found, for example, at col. 3, lines 55-65 of Truett II, in the description of the synthesis of the general formula

Q—CONH—B—C(O)—Z—A

where Q is a quinolone, B is a beta lactam, and A is a third antibiotic, such as vancomycin."

Appellant argues that neither Truett I, nor the examiner, is concerned with the addition of a third antibiotic moiety to any of the bi-component compounds that may be produced according to the disclosure of Truett I. Appellant states that the examiner has suggested the substitution of one of the moieties of Truett I with one of the three moieties disclosed in Truett II. Appellant states that by removing one of the moieties in Truett II, the composition of three antibiotics, which is the focus of the reference, would be destroyed. Appellant argues that Truett II teaches linking vancomycin to ceftazidime, but only in the where vancomycin is simultaneously linked to a third antibiotic.

In Section 4, appellant argues that the three references of Boeckh, Renoud-Grappin, and Staroske, fail to remedy the deficiencies of Truett I and Truett II. For example, nothing in any of Boeckh, Renoud-Grappin, and Staroske would have led one of ordinary skill in the art away from the direct teachings in Truett II to employ a three-component antibiotic compound.

Appellant's arguments filed 6/28/2005 have been fully considered but they are not persuasive.

In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the Reply to the previous Office action, entered 6/28/2005, appellant argues that the references must be considered as a whole. The examiner respectfully submits that appellant's arguments, in actuality, do not do this. The references, taken as a whole, teach and suggest heteromers of antibiotic compounds. Truett, in Truett I, teaches that the linking of two antibiotic moieties functioning in different ways and states:

> It has been realized that the linking of two antibiotic moieties functioning in different fashions, as for example inhibiting cell-wall synthesis or protein synthesis or DNA synthesis, can be of value. Two antibiotic moieties can also be linked in which one is known to attack Gram positive bacteria and another to attack Gram negative bacteria, and this new entity is of value.

Truett I, at col. 1, lines 24-30. Truett, in the later patent Truett II, teaches compositions of three linked antibiotics, and states:

> The value of a composition wherein a trio of individual antibiotics are joined is that the bacterial infective agent will simultaneously be attacked by agents which are known to attack the cell-wall producing enzyme of the bacteria, and inhibit the DNA gyrase enzyme, and inhibit the enzyme that controls bacterial protein synthesis.

Truett II, at col. 1, lines 21-27. Thus the motivation for using heterodimeric antibiotic compounds of Truett I is closely related and extendable to the heterotrimeric antibiotic compounds of related patent Truett II.

The reference of Truett I teaches and suggests the use of ceftazidime as a member antibiotic of a dimeric compound. Truett I, at col. 2, line 3-col. 3, line 14 lists cephalosporins and related compounds as suitable for inclusion in dimeric antibiotic compounds. Truett I includes naming ceftazidime as a cephalosporins "of particular interest", (Truett I at col. 2, line 60) and provides the structure of ceftazidime, (Truett I at col. 15, lines 1-15). Thus Truett I provides ample motivation for the selection of ceftazidime. Furthermore, one of ordinary skill in the art would be motivated to use ceftazidime in the heteromeric antibiotic compounds as taught by Truett, because ceftazidime was a recognized antibiotic drug with demonstrated efficacy. Also, the examiner respectfully submits that would one of ordinary skill in the art would be motivated to use any or all of the 69 specifically disclosed compounds of the 9 disclosed classes of antibiotics, and vancomycin, because of their predictable efficacy as recognized drugs and because 69 specific, known compounds does not represent an

unreasonable number, in and of itself, to use in the claimed invention of the prior art reference of Truett I.

The examiner respectfully submits that appellant's argument that Truett I "was filed at a time when vancomycin was well-known in the art, i.e., 1995, yet fails to mention vancomycin or even the general class of antibiotics to which it belongs," is a further example of attacking the references individually, because another prior art reference, that of Truett II, explicitly teaches vancomycin prior to the filing date of the instant application. Whether vancomycin was well known as of the date that the particular reference of Truett I was filed or published is not relevant to the instant rejection for obviousness. The prior art reference of Truett II taught a trimeric antibiotic compound where vancomycin is linked to a lactam, such as a cephalosporin. The reference of Boeckh et al., taught that vancomycin, in combination with ceftazidime, was frequently administered to cover a broad spectrum of gram-positive and gram-negative bacteria in serious infections in neutropenic cancer patients, (Boeckh et al., at p. 92, para 1 and p. 94, para 4). This relates to Truett I teaching of linking two different antibiotics in order to target both gram-positive and gram-negative bacteria. Boeckh et al., at p. 94, para 4, state: "In summary, the combination of vancomycin and ceftazidime is an effective regimen to compensate for the poor antistaphylococcal activity of ceftazidime alone [citation omitted]". The reference of Staroske et al., teaches synthesis of covalent homodimers of vancomycin. Thus vancomycin, vancomycin covalently linked to cephalosporins, administration of a combination of vancomycin and

ceftazidime, as well as dimers of vancomycin were taught and suggested in the prior art at the time the claimed invention was made.

Thus the combination and linking of vancomycin and cephalosporins, as well as the particular cephalosporin, ceftazidime, (as taught by Truett II and Boeckh et al.), are taught by the prior art. One of ordinary skill in the art would have been motivated to link vancomycin with ceftazidime, as taught by the prior art of Truett II, to form a heterodimeric antibiotic compound comprising a cephalosporin, such as ceftazidime, (and as taught by Truett I), to create a composition of ceftazidime and vancomycin for use as a broad spectrum antibiotic effective against gram-positive and gram-negative bacteria, as suggested by both Truett I and Truett II, by and Boeckh et al. One of ordinary skill in the art would have been motivated to create a covalent link between antibiotics, as taught by Truett I, Truett II, Staroske et al., and the reference of Renoud-Grappin et al., which all teach the covalent linkage of antibiotics. Staroske et al., at 4917, para 1, and Renoud-Grappin et al., at p. 208, para 2, teach the covalent linkage of antibiotics to control the geometry or spacing of the antibiotics in their relationship to receptors, for example, in the cell-wall precursor (Staroske et al).

As further indication of appellant's arguments improperly attacking the references individually, the examiner respectfully notes the structural division of appellant's argument (Sections 1-4), wherein the arguments attack the reference of Truett I in Section 1, the reference of Truett II in Section 2. In Section 4, appellant's argument collectively dismisses the references of Boeckh, Renoud-Grappin and Staroske as teaching, for example, nothing that "would have led one of ordinary skill in the art away

from the direct teaching in Truett II to employ a three-component antibiotic compound", (Reply at p. 11, Section 4). This argument attacks Truett II for teaching trimeric compounds, but ignores the fact that Truett I taught dimeric compounds, as in the instantly claimed invention. The examiner respectfully submits that appellant's arguments dismiss any motivation to make the claimed invention by narrowly restricting consideration of each reference in a piecemeal fashion, instead of considering the cited prior art as a whole.

Appellant's argument that that the examiner is "picking and choosing" components and not compositions is not persuasive, because the prior art of Truett II and Boeckh et al., teach combining vancomycin and ceftazidime, either as part of a heterotrimeric antibiotic compound, or in simultaneous administration into a human, respectively.

(10) Response to Argument

A. Appellant argues that the examiner has failed to establish a prima facie case of obviousness. Appellant states that establishing a prima facie case of obviousness requires (1) that all elements that are disclosed by prior art references, (2) that there exists some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings, and (3) that there is a reasonable expectation of success (Reply Brief at p. 10, citing MPEP 2143).

Appellant argues that modifying the compounds of Truett II would destroy the intended function of the disclosed compounds of Truett II, thereby eliminating any motivation to modify.

Appellant argues that Truett II teaches away from forming a two-component antibiotic comprised of a beta-lactam and vancomycin.

Appellant argues that the obviousness rejection is based on hindsight construction. Appellant argues that Truett I discloses 69 different antibiotic compounds "without any guidance to select one compound above all else. And the Office has not provide any basis to support its contention that one skilled in the art would be motivated to select ceftazidime out of the 69 specifically named compounds disclosed in the reference."

Appellant states:

> In summary, Truett II does not suggest or motivate one skilled in the art to link only ceftazidime and vancomycin because doing so would destroy the basic principle for which the compounds in the reference were designed. Further, by emphasizing particular three-component antibiotics, Truett II teaches away from such a combination. And, as a whole, Truett I provides no suggestion or motivation to select ceftazidime over any of the other 69 compounds disclosed in the reference.

Brief at p. 16.

Appellant further argues Boeckh, Renoud-Grappin, and Staroske do not cure the deficiencies in Truett I and II. Brief at p. 11.

Appellant argues that the Reply, entered 6/28/2005, did in fact traverse the rejection based on the combination of the references as a whole, and did not argue the

references individually, as stated the examiner's argument found in the final Office action, (see, Brief at p. 11).

Appellant's arguments are considered below.

The examiner respectfully notes that the appellant argues that the examiner fails to demonstrate suggestion or motivation to modify or combine the reference teachings, but does not appear to state that all elements have not been disclosed by prior art references, or that there is no reasonable expectation of success, (*compare*, Truett II at the abstract, disclosing processes for preparing compounds having two or three antibiotic functionalities using quinolone derivatives, β-lactams and vancomycin and the like as starting materials and compounds thereof).

Modifying Truett II Would Destroy the Intended Function of the Disclosed Compounds

B. Appellant argues that Truett II provides no motivation to link only a beta-lactam antibiotic to vancomycin. Brief at p. 12. Appellant argues, that "considering Truett II as a whole, the reference would, at best, motivate one of skill in the art to link a beta-lactam antibiotic to vancomycin only when a third quinolone antibiotic is part of the composition." Brief at p. 12.

Appellant argues that modifications based on Truett II would destroy the intended function of the disclosed compounds, (Brief at p. 12, citing Truett II at col. 1., lines 22-

27, col. 1, lines 28-31, col. 24, line 50 to col. 25, line 43; citing *In re Fritch*, 972, F.2d 1260, 1265 n.12, 23 U.S.P.Q.2d 1780, 1783 n. 12 (Fed Cir. 1992); *In re Ratti*, 270 F.2d 810, 813, 123 U.S.P.Q. 349, 352 (C.C.P.A. 1959)). Appellant states: "Here, because the alleged success in using an antibiotic comprising a beta-lactam antibiotic comprising a beta-lactam antibiotic and vancomycin is derived **only** with the inclusion of a quinolone antibiotic, there is no evidence that linking a beta-lactam antibiotic will work for its intended purpose", (Brief at p. 13).

The examiner respectfully submits that appellant's arguments are not persuasive. The examiner respectfully submits that appellant has not provided evidence or reasons as to why an obvious dimeric antibiotic composition of a beta lactam and vancomycin would represent a modification to the trimeric antibiotic composition of Truett II such that the antibiotic composition would not work for its intended purpose.

The examiner respectfully submits that the intended purpose of antibiotic dimers, as taught by the prior art, is the same as the intended purpose of antibiotic trimers, as taught by Truett II. Truett II, contemplates that the value of the disclosed composition is that the bacterial infective agent will be simultaneously attacked by the linked trio of agents which are known to attack the cell-wall producing enzyme of the bacteria, and that emergence of resistance against the antibiotics will be prevented.

Truett II states:

> The value of a composition wherein a trio of individual antibiotics are joined is that the bacterial infective agent will simultaneously be attacked by agents which are known to attack the cell-wall producing enzyme of the

> bacteria, and inhibit the DNA gyrase enzyme, and inhibit the enzyme that controls bacterial protein synthesis.
>
> The value of this composition of three antibiotic functional types is that it will further be seen that resistant strains will be very unlikely to develop due to the necessity of simultaneously overcoming three attacking agents.
>
> Truett II, US 6,437,119 B1, at col. 1, lines 13-28.

These same "values", which the examiner respectfully submits are tantamount to uses or functions, are also attributed to compositions that are made by linking two antibiotic moieties, as taught by the cited prior art. In particular, the primary reference of Truett I, US 5,693,791, teaches that the linking of two antibiotic moieties functioning in different fashions, can be of "value", i.e., useful, (Truett I at col. 1, lines 24-27). In the Background of the Invention Section, Truett I states:

> It has been realized that the linking of two antibiotic moieties functioning in different fashions, as for example inhibiting cell-wall synthesis or protein synthesis or DNA synthesis, can be of value.

Truett I, at col. 1, lines 24-27. Truett I states that "[t]he linked antibiotics are to be utilized in treating various infections in man and animals", (Truett I at the abstract, col. 7, lines 51-53).

The examiner respectfully notes that these uses are substantially the same uses that the instant specification discloses for the claimed invention. For example, the instant specification states:

> The linkers used in this invention are selected to allow multivalent binding of ligands to the ligand binding sites of an enzyme involved in cell wall biosynthesis and metabolism, a precursor used in the synthesis of the bacterial cell wall and/or the cell surface, whether such sites are located interiorly, both interiorly and on the periphery of the enzyme structure, or at any intermediate position thereof.

Specification at p. 38, lines 5-9.

Also, Renoud-Grappin et al., teach the desirability of using heterodimers of linked anti-HIV compounds (see Fig. 4) for reasons that include prevention of drug resistance emergence, (and as contemplated by Truett II). Renoud-Grappin et al., state:

> To prevent the emergence of drug-resistant virus strains, various drugs can be combined. Combined use has been advocated for three main reasons: (i) additive or synergistic antiviral activity; (ii) diminished toxicity; and (iii) reduced risk of drug resistance development. The current tendency is to combine a NNRTI [non-nucleoside reverse transcriptase inhibitor] with a NRTI [nucleoside reverse transcriptase inhibitor]. Thus, the combination of TIBO with either AZT or ddI was found to result in a synergistic inhibition of HIV-1 replication. HIV-I strains that are resistant to NNRTIs are still sensitive to NRTIs and vice versa. Also, HIV-1 strains resistant to AZT or ddI show amino acid substitutions in the HIV-I RT that are distinct from those reported in NNRTI-resistant HIV-I strains. Combinations of anti-HIV agents are now being explored as therapeutic modalities to prevent emergence of virus drug resistance. A rationale toward drug combination may be based on the choice of those drugs that lead to mutually non-complementary or, even better, mutually antagonistic drug resistance mutations. For example, it appears that the AZT resistance mutation (at position 215) and the pyridinone or nevirapine resistance mutations (at position 181) are mutually suppressive. [Citations omitted].

Renoud-Grappin et al., at pp. 207-08, bridging paragraph.

In this regard, the examiner respectfully notes that Truett II, in the Background of the Invention, also contemplates the treatment of AIDS patients using AZT and DDI. Truett II states:

> There is evidence for this statement in the present day success of several cocktails--combinations--of drugs which are being utilized to treat AIDS patients, TB patients and other similar examples. In the case of the AIDS virus, a combination of two retroviral inhibitors, as AZT and DDI are being employed plus one of several viral protease inhibitors as invirase. In the case of TB patients a cocktail of four drugs is being utilized successfully to overcome resistant TB strains.

Truett II, at col. 1, lines 32-40.

Thus, the examiner respectfully submits that one of ordinary skill in the art, in a fair reading, would not find that the modification of the trimeric compound of Truett II, would result in a dimeric compound that would not work for its intended purpose.

Furthermore, the examiner respectfully submits that one of skill in the art would not find that the dimeric compound of the *primary* reference of *Truett I*, would be rendered inoperable by the modification of substituting a vancomycin compound into the dimeric compound. One of ordinary skill in the art would have a reasonable expectation of success in making such a dimeric compound, as the *secondary* reference of Truett II, at col. 23, lines 1-48, col. 26, line 29-col. 27, line 5, teaches the chemistry for linking of a beta-lactam vancomycin to a beta-lactam antibiotic using chloride linking agents. Appellant's arguments provide no evidence or argument that a quinolone derivative is required for the linking of vancomycin to a beta-lactam antibiotic using such chemistry. Appellant arguments provide no evidence or argument that a dimeric beta-lactam-vancomycin compound thereby produced, would not work for its intended purpose.

Truett II Teaches Away From Forming an Antibiotic of a beta-Lactam Linked to Vancomycin

C. Appellant argues that Truett II teaches away from forming a two-component antibiotic comprised of a beta-lactam and vancomycin, and therefore "fails to provide

any motivation to modify its teaching to reach the claimed invention", (Brief at pp. 13-14).

The examiner respectfully submits that appellant's arguments are not persuasive. The examiner respectfully submits that the reference of Truett II, as well as the referenced prior art, does not indicate that a beta-lactam-vancomycin composition would have been contrary to the accepted wisdom of the prior art. The linked antibiotics of Truett II are structurally similar to the instant compound. The examiner respectfully submits that Truett II, at most, does not disclose an anticipatory composition of a beta-lactam linked only to vancomycin. But, as quoted above, Truett II, at col. 1, lines 32-40, teaches that combinations of drugs, such as a cocktail of two retroviral inhibitors, was known in the prior art. Furthermore, Truett II reports the prior art teaches that compositions containing two linked antibiotics are effective in treating disease. Truett II states:

> White, U.S. Pat. No. 5,281,703, has shown that a composition containing a Cephalosporin and a Quinolone antibiotic is very effective in treating certain pneumonias. Pirie, U.S. Pat. No. 4,351,840, has also shown that the composition of a Penicillin with a Beta-lactam protective inhibitor enhances the value of Penicillin.

Truett II, at col. 1, lines 40-46. Therefore, the examiner respectfully submits that Truett II does not teach away from the claimed invention.

The Obviousness Rejection Is Based on Hindsight Construction

D(1) Appellant argues that the obviousness rejection is based on hindsight construction. Brief at p. 14. Truett I does not disclose linking ceftazidime with vancomycin. Brief at p. 14. Appellant argues that Truett I discloses a large number of antibiotic compounds that may be linked together according to the invention of Truett I, but appellant notes that none of the antibiotic compounds is vancomycin. Brief at p. 14. Appellant notes that Truett I discloses nine general classes of antibiotic compounds and 69 specifically named compounds within those classes that may be linked together. Brief at pp. 14-15, citing Truett I at col. 1, line 46-col. 6, line 27. Appellant argues "the Office must provide a basis for the initial selection of a single one of the 69 specific compounds, i.e., ceftazidime, from among all the other antibiotic compounds disclosed in the reference." Brief at p. 15. Appellant argues that "[i]n face of this limited guidance, and the lack of any disclosure regarding vancomycin, Applicants respectfully submit that one or ordinary skill in the art reading the general teachings of Truett I would have found nothing to motivate or guide them to prepare a compound containing both a beta-lactam and vancomycin composition as proposed by the Office." Brief at p. 16.

The examiner respectfully submits that appellant's arguments are not persuasive. Initially, the examiner respectfully notes that the claims are generically drawn to various genera of beta-lactam ligands, which encompass the species ceftazidime that is taught by cited prior art references.

In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The examiner respectfully submits that there were a multitude of microbial agents at the time of the claimed invention, as was taught by Truett I, which states:

> This invention [of Truett I] is concerned with the preparation of a wide variety of antibiotics of new and novel structure and antimicrobial activity. The compounds thus prepared are products from the linking of diverse antibiotic moieties via difunctional organic compounds such as diisocyanates, dianhydrides, diacidchlorides, diepoxides and carbodiimides, said antibiotics being drawn from the classes of compounds sulfonamides, penicillins and related, cephalosporins and related, quinolones, chloramphenicol, erythromycins, metronidazole, tetracyclines and aminoglycocides.
>
> The medical literature regarding antimicrobial agents is vast and describes a number of antimicrobials including naturally occurring compounds as well as synthetic or semisynthetic compounds produced in the organic laboratory. These antimicrobial agents are classified as noted above, and there are many classes in addition to the above-noted ones.

Truett I at col. 1, lines 5-20.

The examiner respectfully submits that the choice of ceftazidime as one of 17 cephalosporins, all of which share a common molecular ring structure, (Truett I at col. 2, line 49-col. 3, line 14); and wherein cephalosporins are one of 9 classes of antibiotics,

does not represent such an unreasonable or arbitrary a choice for one of ordinary skill in the art, so as to be non-obvious, relative to the vast number of antibiotics. The examiner respectfully submits that appellant's argument focusing on the mere number of specifically named compounds (i.e., 69), does not take into account the guidance provided by Truett I, in its disclosed classification of antibiotics based upon common molecular structure. Furthermore, both Truett II and Boeckh et al., teach the combination of ceftazidime and vancomycin, as discussed below.

D(2) Appellant argues that the publications of Boeckh et al., Renoud-Grappin et al., and Staroske et al., do not provide any motivation to link ceftazidime and vancomycin. Staroske et al., discloses vancomycin can be linked to other compounds but do not provide motivation to link ceftazidime and vancomycin. Renoud-Grappin et al., "simply discloses linking two drugs, none of which are antibiotics". Brief, at pp. 16-17.

The examiner respectfully submits that appellant's arguments are not persuasive. Boeckh et al., at p. 92, para 1, teach that vancomycin is used in combination with ceftazidime as a broad spectrum treatment for gram positive and gram negative bacterial infections. This compares to the primary reference of Truett I, which in The Background of the Invention Section, states:

> Two antibiotic moieties can also be linked in which one is known to attack Gram positive bacteria and another to attack Gram negative bacteria, and this new entity is of value.

Truett I, at col. 1, lines 27-30. This further compares to the secondary reference of Truett II, which teaches the linkage of the cephalosporin, ceftazidime, with vancomycin as part of a heterotrimeric compound, which also includes quinolone.

In regard to linking antibiotics to form a heterodimer, Renoud-Grappin et al., suggest linking antibiotics of different classes by spacers of appropriate length to produce heterodimers that cooperatively target proximal binding sites in order to combine the inhibitory capacity of the two different antibiotic classes.

> One approach to combination therapy, which has been suggested by Nanni et al. (1993) is the use of heterodimers resulting from the linking of a NNRTI and a NRTI through an appropriate spacer, in an attempt to combine the inhibitory capacity of these two different classes of molecules. There are several attractive features to such an approach. These inhibitors might be highly specific for HIV-1 RT owing to their non-nucleoside moiety. The two binding sites (catalytic site of DNA polymerization on one hand and the allosteric site of NNRTIs on the other) are sufficiently proximal (Fig. 3) (Kohlstaedt et al., 1992) that they can be spanned by a single heterodimer inhibitor, as shown in Fig. 4. It is also likely that these heterodimer compounds could be extremely interesting and powerful probes of the catalytic mechanisms of DNA polymerization. By appropriate choice of spacer length, it may be possible to freeze DNA polymerization. Current knowledge of the HIV-I RT [reverse transcriptase] structure suggests a minimum distance of approximately 17 Å between the two inhibitor-binding sites. Experiments carried out with a variety of NNRTIs demonstrate the cooperation between the nucleoside binding site and the allosteric site occupied by non-nucleoside inhibitors (De Clercq, 1992).

Renoud-Grappin et al., at p. 208 para 2.

Furthermore, Renoud-Grappin et al., at pp. 207-08, bridging paragraph, teach the use of heterodimers of AZT linked to DDI in anti-HIV compounds. As noted above, both Truett II, and Renoud-Grappin et al., (at pp. 207-08, bridging paragraph), contemplate the treatment of AIDS patients using AZT and DDI.

Staroske et al., at p. 4917, para 3, and the abstract, suggest the use of homodimers of linked vancomycin because the development of vancomycin-resistant bacteria provides incentive for the development of more potent antibiotics and because dimers have the potential to exploit additional cooperative interactions when binding to bacterial cell-wall precursors at a surface. Staroske et al., at p. 4917, para 1, teach the glycopeptide antibiotics vancomycin and teicoplanin were the current drugs of choice against antibiotic-resistant bacteria.

D(3) Appellants note that Boeckh et al., while disclosing the combination of ceftazidime and vancomycin as separate compounds, is not directed to linking the two together. Appellants argue that Boeckh et al., specifically discloses that previous studies show "excellent clinical response to the combination of vancomycin and ceftazidime," as separate compounds, (see Boeckh et al., at p. 94, right column). Appellant states:

> One of ordinary skill in the art, considering Broeckh as a whole, would conclude that the reference discloses the use of ceftazidime and vancomycin as separate compounds within a mixture without any apparent disadvantages, including any inconveniences. Accordingly, that skilled artisan would have no motivation to modify Broeckh's composition by linking ceftazidime to vancomycin, as required by the Appellants' invention. *See Winner Int'l Royalty Cor v. Wang*, 202 F.3d 1340, 1349, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000) (where the Federal Circuit upheld a finding of no motivation to combine references when there was no apparent disadvantage to using the method disclosed in one of the prior art references.).

Brief, at p. 17.

The examiner respectfully submits that Boeckh et al., does not stand for the proposition that the combination cocktail of ceftazidime and vancomycin is perfected to the degree such that one of ordinary skill would not be motivated to modify the composition of Boeckh et al. The examiner respectfully submits that appellant's arguments over interpret the teachings of Boeckh et al. The reference of Boeckh et al., which has a publication date of Jan. 1988, taught that the ceftazidime and vancomycin combination cocktail, while effective to treat infections in neutropenic cancer patients, had not been completely studied. Boeckh et al., state:

> The renewed clinical interest in vancomycin is due to the increasing importance of Staphylococcus epidermidis and Staphylococcus aureus infections, especially in immunocompromised patients. The pharmacokinetics of vancomycin have been studied extensively, especially in patients with various degrees of reduced renal function. However, pharmacokinetic data of patients with normal renal function have mostly been obtained in very few patients. Furthermore, vancomycin is frequently used in serious infections in neutropenic cancer patients in combination with ceftazidime to cover a broad spectrum of gram-positive and gram-negative bacteria. However, possible microbiological and pharmacokinetic interactions of this combination have not been studied. Therefore, we examined the pharmacokinetics and serum bactericidal activity of vancomycin-ceftazidime. [Citations omitted].

Boeckh et al., at p. 92, para 1. In light of these teachings, the examiner respectfully submits that one of ordinary skill in the art would not conclude that the cocktail combination of ceftazidime and vancomycin was so without any apparent disadvantage or inconvenience, that no further need for pharmacologic or medicinal modification would reasonably be suggested or considered.

D(4). Therefore, examiner respectfully submits that one of ordinary skill in the art would have been motivated to make heterodimers of ceftazidime linked to vancomycin because the combination of ceftazidime linked to vancomycin was desirable for broadly attacking both Gram positive and Gram negative bacteria; desirable because linking different antibiotics would permit cooperation in targeting proximal binding sites; desirable because the combination of ceftazidime and vancomycin was particularly effective for treating infections; and desirable because heterodimeric and homodimeric linked antibiotics, containing cephalosporins (as taught by Truett I and Truett II), such as the cephalosporin ceftazidime, (Truett I), and the glycopeptide antibiotic vancomycin, (Truett II), were considered to prevent the emergence of antibiotic resistance.

The Office's Additional Remarks in the Final Rejection Do Not Support a Prima Facie Case of Obviousness

E. Appellant, in referring to the previous Office action, takes exception to the statement "the motivation for using heterodimeric antibiotic compounds of Truett I is closely related and extendable to the heterotrimeric antibiotic compounds of related patent Truett II", (Brief at p. 17). Appellant argues "[w]hile there may be a general desire in the art to create broad spectrum antibiotics, this general desire alone is not enough to provide motivation to link the two specific antibiotics of the claimed invention." Appellant argues that the only teaching is to link ceftazidime and vancomycin in combination with a quinolone, and dissection of the quinolone would destroy the

teaching of Truett II. Appellant argues that the examiner has "simply taken the position that you can select a beta-lactam moiety from Truett I and combine with vancomycin from Truett II", and that such a view is too simplistic and does not take into account the references as a whole. Appellant argues that the examiner has used hindsight knowledge of the presently claimed invention, and has not explained why one of ordinary skill in the art would have been to modify the teachings of Truett I and Truett II in the manner suggested by the examiner.

The examiner respectfully submits that appellant's arguments are not persuasive. The examiner respectfully submits that these arguments are cumulative of the previously presented arguments, and are not persuasive for the reasons set forth above.

In regard to appellant's traversal against the statement that "the motivation for using heterodimeric antibiotic compounds of Truett I is closely related and extendable to the heterotrimeric antibiotic compounds of related patent Truett II", the examiner again respectfully notes the similarities of the structures of linked antibiotic compounds taught by Truett I, col. 1, lines 45-50 and Truett II, col. 3, lines 1-5.

In regard to appellant's argument that "[w]hile there may be a general desire in the art to create broad spectrum antibiotics, this general desire alone is not enough to provide motivation to link the two specific antibiotics of the claimed invention", the examiner respectfully submits that these arguments are addressed in the above

Response to Arguments subsection entitled "The Obviousness Rejection Is Based on Hindsight Construction".

In regard to appellant's argument that the only teaching is to link ceftazidime and vancomycin in combination with a quinolone, and dissection of the quinolone would destroy the teaching of Truett II, the examiner respectfully submits that these arguments are addressed in the above Response to Arguments subsection entitled "Modifying Truett II Would Destroy the Intended Function of the Disclosed Compounds".

In regard to appellant's argument that Appellant argues that the examiner has "simply taken the position that you can select a beta-lactam moiety from Truett I and combine with vancomycin from Truett II", and that such a view is too simplistic and does not take into account the references as a whole, the examiner respectfully submits that these arguments are addressed in the above Response to Arguments subsection entitled "The Obviousness Rejection Is Based on Hindsight Construction".

In regard to appellant's argument that Appellant argues that the examiner has used hindsight knowledge of the presently claimed invention, and has not explained why one of ordinary skill in the art would have been to modify the teachings of Truett I and Truett II in the manner suggested by the examiner, the examiner respectfully submits that these arguments are addressed in the above Response to Arguments subsection entitled "The Obviousness Rejection Is Based on Hindsight Construction".

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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